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(54) Title: METERING AND PACKAGING OF CONTROLLED RELEASE MEDICATION

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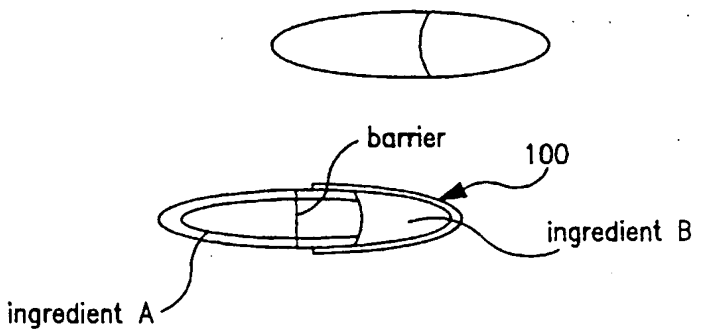

(57) Abstract: Controlled quantities of powdered medication are formed in controlled release packages using electrostating metering. Also provided are combination medication therapy delivery packages comprising two or more active pharmaceuticals segregated from one another in a single delivery package.

Additionally, many experts believe controlled release drug delivery has many important non-therapeutic ramifications as well, including a financial saving to the patient in terms of fewer lost work days, reduced hospitalization and fewer visits to the physician.

It is known that certain design parameters are critical to proper drug delivery. Typically, they are: (1) delivering the drug to the target tissue; (2) supplying the drug for a predetermined period of time; and (3) fabricating a delivery system that provides drug in the desired spatial and temporal pattern. Controlled release drug delivery systems are intended to utilize these parameters to achieve the aforementioned advantages as compared to conventional pharmaceutical dosing.

Previously direct placement of medication onto a substrate generally was limited to medical placement of large doses or required technology where the active pharmaceutical was mixed with the substrate or matrix to provide differential delivery, or coated with a material with desired release characteristics.

As used herein "controlled-release" is used to describe a system, i.e. method and materials for making an active ingredient available to the patient in accordance with a preselected condition, i.e. time, site, etc.. Controlled-release includes the use of instantaneous release, delayed release and sustained release. "Instantaneous release" refers to immediate release to the patient. "Delayed release" means the active ingredient is not made available until some time delay after administration. Typically, dosages are administered by oral ingestion, although other forms of administration are contemplated in accordance with the present invention. "Sustained release" refers to release of active ingredient whereby the level of active ingredient available to the patient is maintained at some level over a period of time. The method of effecting each type of release can be varied. For example, the

which the therapeutic agent leaches out, through a diffusion controlled process. Conventional SR formulations are generally designed to release their active ingredients over an extended period of time, usually 8-24 hours. Conventional SR formulations use waxes or hydrophilic gums as the primary drug carriers to prolong the release of the active ingredients.

Starch USP (potato or corn) is commonly used as a component in conventional tablet or hard shell capsule formulations.

The existing sustained release technologies generally involve relatively complicated formulations and manufacturing processes which often are difficult and expensive to precisely control. For example, one well known SR delivery system, OROS, marketed by the Alza Corporation, involves laser drilling through a tablet to create passages for the release of the drug from the tablet core. In controlled release technologies, it is desirable to be able to incorporate the active ingredient in its controlled-release pattern in a single dosage unit without deteriorating the active ingredient. Moreover, the dosage unit should be able to deliver the system without interfering with its release pattern.

Various methods have been devised to enable controlled-release systems to be delivered to a patient without destruction of the delivery system during manufacturing, handling and distribution. For example, controlled-release systems have been provided in the form of beads or particles which are packaged in a gelatin capsule for oral dosage. This method of delivery of the controlled-release system prevents damage to the coating on the beads.

Furthermore, when controlled-release active ingredients are incorporated in compression tablets, it may be difficult for many people to swallow such tablets. Moreover, dissolution of high compression tablets often initially is slow and erratic and may result in localized hot spots of alimentary tract irritation where disintegration and release of the active ingredient finally

area. Alternatively, a predetermined amount of powdered pharmaceutical or drug may be deposited directly in a package using electrostatic charge technology.

When a given amount of a powdered pharmaceutical or drug is to be packaged, the charge and area of charge can be determined experimentally for each dose of pharmaceutical or drug and each particle size distribution. This can be done by controlling either the charged area for a given charge density or the total electrostatic charge on any individual charged area. These conditions can be adjusted to provide essentially the exact desired amount of the particular pharmaceutical or drug to be transferred at the transfer station.

In our U.S. Application Serial No. 09/097,104, we describe another electrostatic charge technology which may be adopted to be used for measuring and packaging unit doses of a pharmaceutical or drug in a readily ingestible form, i.e. as a tablet or capsule. The technology thus described also permits reproducible precise measurement and packaging of a pharmaceutical or drug, and which may be scaled from laboratory to pilot plant to full scale production without the need for recertification.

In accordance with one aspect of the present invention, controlled quantities of powdered medication are formed in controlled release packages using electrostatic metering technology. The present invention also provides, in another aspect, combination medication delivery systems in which the active ingredients are segregated from one another

Further features and objects of the present invention will become clear from the following detailed description taken in conjunction with the accompanying drawings, wherein like numerals depict like parts, and wherein:

Fig. 1 is a schematic flow diagram showing the various steps involved in practicing the present invention;

passed to a powder discharging device 30 which discharges the powder 26A from the surface 24 onto a membrane 29. Alternatively, the powder may be placed directly onto the membrane 29. The membrane 29 containing its charge of powder 26A, then passes through a sealing step 32 wherein a second membrane 34 which may be porous, permeable or semi-permeable covers and seals the discharged powder 26A on the membrane 29. There is thus produced an aliquot of powdered medicine 26A sandwiched between semi-permeable or permeable membranes 29 and 34.

This sandwiched material is then passed to a cutting station 38 wherein the sandwich is cut into individual tablets or wafers 36.

As mentioned previously in discussing Fig. 1, the carrier surface with the electrostatic charge carries a known amount of charge on its surface and the polarity of this charge is opposite to that of the powder particles suspended in the chamber. The charged particles migrate to the charged surface because of the attraction by the opposite nature of the charges. This migration of the particles continues until the charge on the carrier surface is neutralized.

The actual amount of powder mass transferred to the carrier surface is a function of the mass-to-charge ratio of the charged particles. Although it is difficult to achieve a linear relationship between the mass and the actual charge, it is possible to establish a fixed relationship between the surface area of the powder particles and the charge the powder particle is carrying at charge saturation. However, the surface area of a mixed group of powder particles of different sizes and shapes can be extremely difficult to calculate mathematically, particularly when the shapes are irregular, (e.g. non-spherical, microcrystalline, etc.) As mentioned earlier, the simplest method of determining the amount and area of charge to attract a given weight of particles is to estimate the correct area and charge and then apply the estimated charge to the estimated area on the carrier surface 24 and expose

50, 52, encapsulated between membranes 29 and 34 for simultaneous controlled release.

Alternatively, as shown in Fig. 5, two different drugs 60, 62 may be layered on one another, separated by a membrane 64 so the two medications may be delivered sequentially either in the same location, or in different locations within the alimentary canal. Another feature and advantage of the multi-drug tablet of Fig. 4 and Fig. 5, as will be discussed in detail herein below, is that two normally incompatible drugs may be to be safely packaged in a single tablet.

The invention is susceptible to modification. For example, individual doses may be formed by electrostatic deposition in accordance with U.S. Patent No. 5,714,007.

Other possibilities are possible. For example, referring to Fig. 6, the tablet 70 may incorporate an adhesive layer 72 such as a mucosal adhesive, which in turn is covered by an acid or alkaline dissolvable protective membrane 74, which dissolves at a selected site allowing the adhesive to adhere, for example, to the intestinal wall, thereby increasing residence time of the medication in a chosen location. Alternatively, an acid or alkaline activatable adhesive may be applied to the outer surface of the tablet. In yet another possibility, the membrane may be a material which expands on contact with the acid or alkaline in the alimentary canal and becomes more porous whereby to slowly release medication in a chosen location within the alimentary canal.

As mentioned above, a particular feature and advantage of the present invention is that it permits packaging, within a single tablet of two or more different drugs normally considered to be incompatible. Certain drugs are known to cause undesirable side effects which need to be countered by a second drug. For example, Omeprazole[1] which finds substantial utility as an oral antiulcer agent, also is known to block the release of B12 from its protein

question of chemical interaction. Thus, several drugs are normally prescribed as separate tablets or capsules which presents a problem in terms of patient compliance, e.g. TB triple therapy, AIDS multi-drug therapy, anti-infectives, etc. Also, delivery of two or more active medicaments could reduce side effects, and/or improve therapeutic response which may in turn permit a decrease in the required dosage.

The combination of drugs of the present invention can be grouped into polypharmacy for a therapeutic area, and into polypharmacy for treatment of co-morbid diseases. The invention will now be described with reference to the following non-limiting examples.

(1) Omeprazole[1] and analogs and isomers – As noted above Omeprazole is an inhibitor of gastric secretion and also inhibits the absorption of certain drugs/compounds that require stomach acid such as Vitamin B12, the deficit of which results in pernicious anemia. A combination of B12 with Omeprazole would eliminate the potential problem.

(2) Valacyclovir[2] and analogs and is used to treat Herpes Zoster. It is well known that two drugs Cimetidine[3] and Probenecid[4] both increase the AUC (area under curve) and Cmax. A combination drug can be constructed with a combination of either one or more of these components to provide more efficacy.

(3) Enalapril[5] and analogs and isomers is an ACE inhibitor used for the treatment of hypertension. This drug has been used with the following and analogs and isomers beta adrenegic-blocking agents, methyldopa, nitrate, calcium blocking agents, Hydralazine[6], Prazosin[7] and Digoxin[8] without clinically significant side effects. One or more of these agents may be combined with Enalapril to improve the compliance of patient with hypertension and hypertension and other cardiac diseases.

(4) Ketoconazole[9] and analogs and isomers is used to treat fungal infections. One of the side effects is the reduction of Testosterone. This side

4. Thiazides and related drugs, e.g. Hydrochlorthiazide[18] and Chlorthalidone[19].

5. A diuretic which is already formulated as a combination diuretic, e.g. Aldactazide, a combination of Spironolactone[20] (potassium sparing diuretic + hydrochlorothiazide). This combination makes use of the different methods of action of two different diuretics separated by a barrier from an ACE inhibitor such as Enalapril maleate[21], Fosinopril sodium[22], or Lisinopril[23].

Combination diuretics such as Zestoretic AstraZeneca a combination of Lisinopril[27] 10 or 20 mg and Hydrochlorthiazide[17] 12.5 or 25 mg, exist in tablet form comprising mixed active ingredients in the pill or tablet form. The present invention segregates the Lisinopril and Hydrochlorthiazide.

In accordance with the present invention, we can form e.g. 10 mg and 20 mg Lisinopril[22] pills, and 12.5 and 25 mg Hydrochlorthiazide[17] pills and then put them together with a barrier between two active ingredients. Pills can be in the form of tablets, pills, capsules or other solid oral dosage forms.

Combination # 2 Diuretic + Angiotensin II Receptor Antagonist

Diuretics as described in combination drug # 1 plus an angiotensin II receptor antagonist such as Losartan potassium[24] and/or Valsartan[25].

These combinations also permit administration of two or more drugs which, if in direct contact, have an unacceptable reaction.

Combination # 3 Diuretic + Beta Adrenergic Blocking Agent

Diuretic as described in combination #1, plus a beta adrenergic blocking agent such as Bioprolol fumarate[26] or Metoprolol succinate[27].

Combination # 4 Diuretic + Calcium chanel block

Diuretic as described in combination #1, plus a Calcium chanel block such as Amlodipine[28] or Nifedipine[29].

Combination # 5 Diuretic + Periferal Adrenergic Blocking Agent

Combination # 12

Short acting oral insulin with sustained release oral insulin.

(11) This example provides various drug combinations for treating hyperlipidemia.

Combination # 13

HMG-CoA reductase inhibitor such as Simvastatin[35], Atorvastatin[36], or Pravastatin[37] with a bile acid sequestrant such as Colestipol hydrochloride[38].

Combination # 14

A HMG-CoA reductase inhibitor with a niacin compound.

Combination # 15

A HMG-CoA reductase inhibitor or combination #14 with a hypolipidemia agent such as Gemfibrozil[39].

(12) This example provides various drug combinations for treating congestive heart failure.

Combination # 16

Digitalis plus an ACE inhibitor with or without a diuretic, and optionally including a beta blocker.

Combination # 17

Digitalis plus any of the combination drugs #1-#7.

(13) This example provides various drug combinations for treating asthma/allergy.

Combination # 18

Rapid onset anti-histamine plus sustained release anti-histamine.

Combination # 19

Antihistamine plus Leukotriene modifier, such as Loratadine[40] plus Montelukast[41].

(14) This example provides a drug combination for treating migraine.

Combination # 20

Triple combination Isoniazid[55] and Pyrazidamide[56] and Rifampin[57].

(20) This example provides a polypharmacy for treatment of co-morbid diseases.

Combination # 28

80% + of diabetics are also hypertensive. Therefore a combination of any of combination drugs # 7-12 which are the combinations for control of the diabetes with any of combination drugs #1-7 or the single component medicaments used in the anti-hypertensive combinations.

Combination # 29

Hyperlipidemia is frequently concurrent with cardiac disease therefore any of combination drugs # 13-17 plus any of combination drugs # 1-7.

(21) This example provides a polypharmacy for treatment of Angina.

Combination #30

A Calcium channel block such as Nifedipine[29] plus a vasodilator such as nitroglycerin.

(22) This example provides a polypharmacy for treatment of seizure disorders.

Combination #31

A Gamma Aminobutyric analog such as Gabapentin[58] or a Gamma Aminobutyric stimulator such as Divalproex Sodium[59] plus a Benzodiazepine such as Alprazolam[60].

(23) This example provides various drug combinations for treating pain and the side effects of opioids:

Combination #32

An opioid and a non-opioid analgesic such as codeine and acetominophine.

Combination #33

An opioid and an antiemetic.

Combination #34

The present invention also allows for the rapid production of different dosage medications using the same active ingredient, and allows for the development of medications with longer resident time.

16. Furosemide: 4-chloro-N-furfuryl-5-sulfamoylanthranilic acid.

17. Aldactone: 17-hydroxy-7*alpha*-mercapto-3-oxo-17*alpha*-pregn-4-ene-21-carboxylic acid *gamma*-lactone acetate.

18. Hydrochlorthiazide: 6-chloro-3, 4-dihydro-2H-1, 2, 4-benzothiadiazine-7-sulfonamide 1, 1-dioxide.

19. Chlorthalidone: 2-Chloro-5-(2,3-dihydro-1-hydroxy-3-oxo-1H-isoindol-1-yl)benzenesulfonamide.

20. Spirolactone: 17-hydroxy-7*alpha*-mercapto-3-oxo-17*alpha*-pregn-4-ene-21-carboxylic acid *gamma* -lactone acetate.

21. Enalapril maleate: (*S*)-1-[*N*-[1-(ethoxycarbonyl) -3-phenylpropyl]-L-alanyl] -L-proline, (*Z*)-2-butenedioate salt (1:1).

22. Fosinopril sodium: L-proline, 4-cyclohexyl-1-[[[2-methyl-1-(1-oxopropoxy) propoxyl](4-phenylbutyl) phosphinyl]acetyl]-,sodium salt, *trans*-.

23. Lisinopril: (S)-1-[N^2-(1-Carboxy-3- phenylpropyl)-L-lysyl]-L-proline dihydrate.

24. Losartan potassium: 2-butyl-4-chloro-1[*p*-(*o*-1*H*-tetrazol-5-ylphenyl)benzyl]imidazole-5-methanol monopotassium salt.

25. Valsartan: as *N*-(1-oxopentyl)-N-[[2'-(1*H*-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-L-valine.

26. Bioprolol fumarate: (±)-1-(4-((2-(1-Methylethoxy)ethoxy)methyl)phenoxy)-3-((1-methylethyl)amino)-2-propanol (*E*)-2-butenedioate (2:1) (salt).

27. Metoprolol succinate: (±) 1-(isopropylamino)-3-[p-(2-methoxyethyl) phenoxy]-2-propanol succinate (2:1) (salt).

28. Amlodipine: (R.S.) 3-ethyl-5-methyl-2-(2-aminoethoxymethyl)-4-(2-chlorophenyl)-1,4-dihyro-6-methyl-3,5-pyridinedicarboxylate benzenessulphonate.

29. Nifedipine: 3,5-pyridinedicarboxylic acid, 1,4-dihydro-2,6-dimethyl-4-(2-nitrophenyl)-,dimethyl ester.

43. Sumatriptan: 3-[2-(dimethylamino)ethyl]-N-methyl-indole -5-methanesulfonamide succinate (1:1).

44. Doperidol: 1-(1-[3-(p-fluorobenzoyl)propyl]-1,2,3,6-tetrahydro-4-pyridyl)-2-benzimidazolinone.

45. Dexamethasone: 9-fluoro-11 β,17,21-trihydroxy- 16α-methylpregna-1,4-diene-3,20-dione.

46. Famotidine: *N*'-(aminosulfonyl)-3-[[[2- [(diaminomethylene)amino]-4-thiazolyl]methyl]thio]propanimidamide.

47. Prozac: (±)-N-methyl-3-phenyl-3-[(α,α,α-trifluoro-*p*-tolyl)-oxy]propylamine hydrochloride.

48. Buptopion: (±)-1-(3-chlorophenyl)-2-[(1,1-dimethylethyl)amino]-1-propanone hydrochloride.

49. Crixivan: is [1(1S,2R),5(S)]-2,3,5-trideoxy-N-(2,3-dihydro-2- hydroxy-1H-inden-1-yl)-5-[2-[[(1,1-dimethylethyl)amino]carbonyl]-4-(3-pyridinylmethyl)- 1-piperazinyl]-2-(phenylmethyl)-D-erythro-pentonamide sulfate (1:1) salt.

50. Sustiva: (S)-6-chloro-4-(cyclopropylethynyl)-1,4-dihydro-4-(trifluoromethyl)-2H-3,1-benzoxazin-2-one.

51. Ziduvudine: 3'-azido-3'-deoxythymidine.

52. Azidothymidine: 3'-azido-3'-deoxythymidine.

53. Cyclosporine: [*R*-[*RR**(E)]] cyclic(L-alanyl-D-alanyl-N-methyl-L-leucyl-N-methyl-L-leucyl-N-methyl-L-valyl-3-hydroxy-N,4-dimethyl-L-2-amino-6-octenoyl-L-α-amino-butyryl-N-methylglycyl-N-methyl-L-leucyl-L-valyl-N-methyl-L-leucyl).

54. Prednisone: pregna-1,4-diene-3,11,20-trione, 17,21-dihydroxy.

55. Isoniazid: isonicotinic acid hydrazide.

56. Pyrazinamide: pyrazinecarboxamide.

57. Rifampin: 3-(4-methyl-1-piperazinyl-iminomethyl)-rifamycin.

CLAIMS

1. A controlled release pharmaceutical delivery package comprising a unit aliquot dose of a pharmaceutical electrostatically deposited on a porous, permeable or semi-permeable ingestible membrane.

2. A pharmaceutical delivery package according to claim 1, wherein said membrane comprises an acid-dissolvable material.

3. A pharmaceutical delivery package according to claim 1, wherein said membrane comprises an alkali-dissolvable material.

4. A pharmaceutical delivery package according to claim 1, and comprising two or more pharmaceuticals deposited on said membrane, and separated by one another by one or more barriers or membranes.

5. A pharmaceutical delivery package according to claim 1, and further comprising an adhesive on the outer surface of the membrane.

6. A pharmaceutical delivery package according to claim 5, wherein the adhesive is acid or alkylene activatable.

7. A pharmaceutical delivery package according to claim 5, and further comprising an alkali or acidic dissolvable membrane covering the adhesive.

8. A pharmaceutical delivery package according to claim 1, wherein said membrane comprises a material which expands upon contact with acid or alkaline in the alimentary canal, whereby to become more porous.

9. A pharmaceutical delivery package comprising two or more active pharmaceuticals (a) combined in a single delivery package, and (b) segregated from one another, wherein said single delivery package comprises an unitary structure for repeatable administration of fixed quantifies of said two or more active ingredients to the user.

23. A pharmaceutical delivery package comprising a combination of a diuretic and a Beta Adrenergic Blocking Agent.

24. A pharmaceutical delivery package comprising a combination of a diuretic and a Calcium channel block.

25. A pharmaceutical delivery package comprising a combination of a diuretic and a Periferal Adrenergic Blocking Agent.

26. A pharmaceutical delivery package comprising a combination of a diuretic and an Adrenergic central stimulant.

27. A pharmaceutical delivery package comprising a combination of a diuretic and Endothelin A.

28. A pharmaceutical delivery package comprising a combination of an ACE inhibitor and a beta blocker.

29. A pharmaceutical delivery package comprising a combination of a biguanide and a sulfonylurea.

30. A pharmaceutical delivery package comprising a combination of a biguanide and a thiazolidinedione.

31. A pharmaceutical delivery package comprising a combination of Metaformin and an alpha glucosidase inhibitor.

32. A pharmaceutical delivery package comprising a combination of a short acting oral insulin with a sustained release oral insulin.

33. A pharmaceutical delivery package comprising a combination of an HMG-CoA reductase inhibitor with a bile acid sequestrant.

34. A pharmaceutical delivery package comprising a combination of an HMG-CoA reductase inhibitor with a niacin compound.

35. A pharmaceutical delivery package comprising a combination of an HMG-CoA reductase inhibitor with a hypolipidemia agent.

36. A pharmaceutical delivery package comprising a combination of an HMG-CoA reductase inhibitor, a niacin compound and a hypolipidemia agent.

50. A pharmaceutical delivery package comprising a combination of a Calcium channel block plus a vasodilator.

51. A pharmaceutical delivery package comprising a combination of a Gamma Aminobutyric analog or a Gamma Aminobutyric stimulator plus a Benzodiazepine.

52. A pharmaceutical delivery package comprising a combination of an opioid and a non-opioid analgesic.

53. A pharmaceutical delivery package comprising a combination of an opioid and an antiemetic.

54. A pharmaceutical delivery package comprising a combination of an opioid and a bowel softener or evacuant.

55. A pharmaceutical delivery package comprising a combination of a cyclooxygenase-2 inhibitor plus Omeprazole.

56. A pharmaceutical delivery package comprising a combination of an anti-inflammatory plus Omeprazole.

57. A pharmaceutical delivery package comprising a combination of prednisone plus testosterone.

58. A pharmaceutical delivery package comprising a combination of prednisone plus estrogen.

59. A pharmaceutical delivery package comprising a combination of a selective serotonin reuptake inhibitor plus a benzodiazepine.

60. A pharmaceutical delivery package comprising a combination of an aminoketone plus Lorazepam.

61. A pharmaceutical delivery package as claimed in any one of claims 13 to 19, and further including digitalis.

62. A pharmaceutical delivery package as claimed in any one of claims 20 to 24, and further including a combination of any of the combinations of any one of claims 13 to 19.

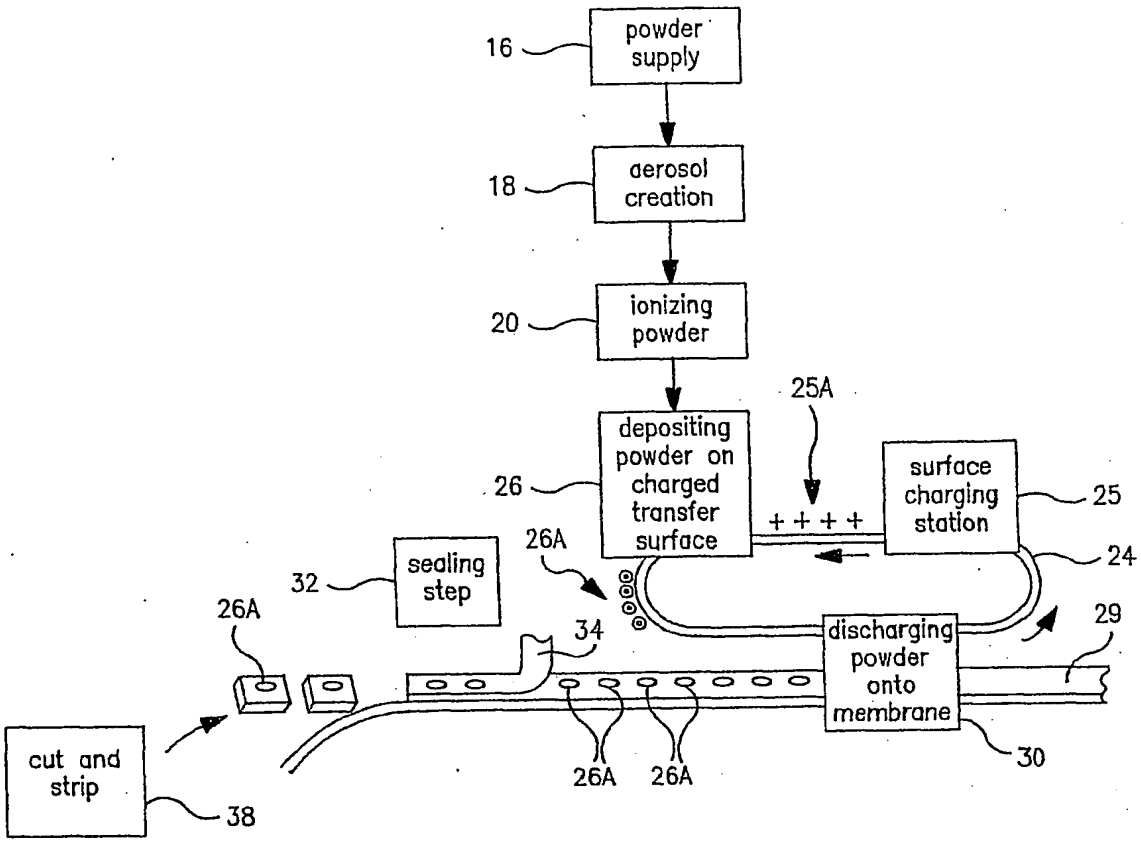

FIG. 1

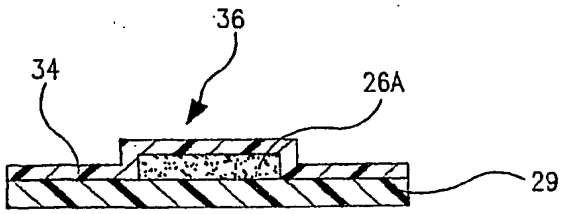

FIG. 2

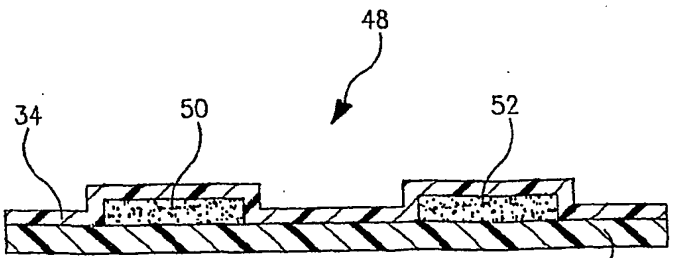

FIG. 4

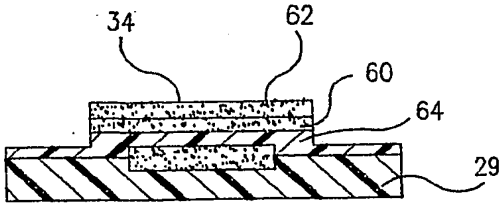

FIG. 5

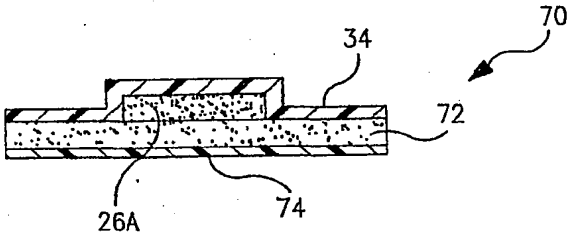

FIG. 6

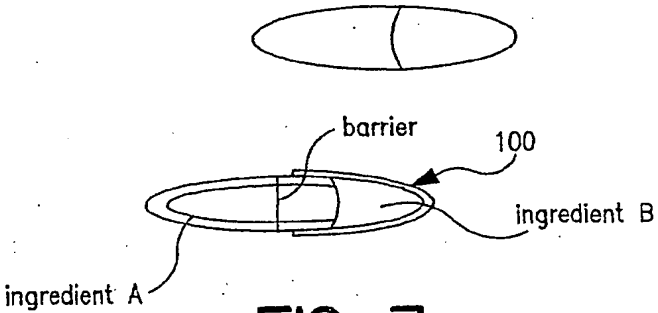

FIG. 7